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Confidence in recommendations based on Network Meta-Analysis: threshold analysis as an alternative to GRADE

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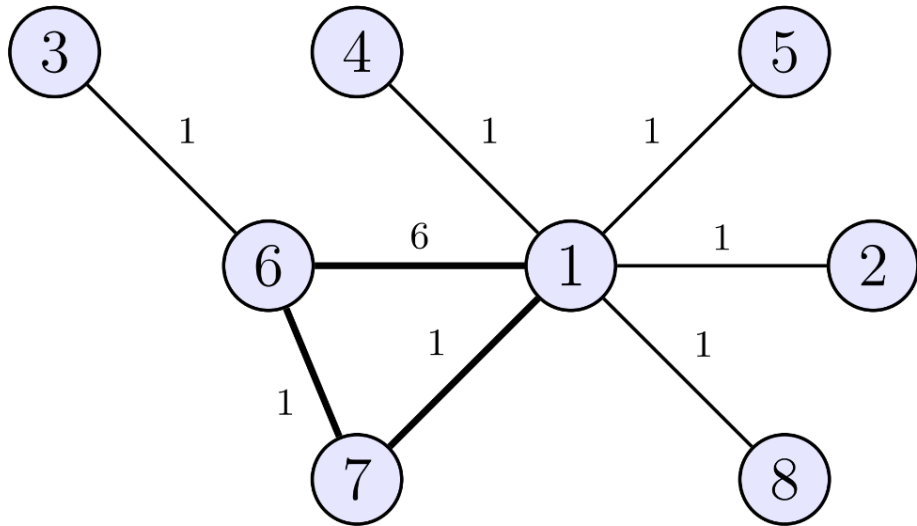
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Background

Network Meta-Analysis (NMA)

- Combines evidence on multiple treatments from several studies
- Arranges treatments on a network structure joined by study evidence
- Provides a consistent set of treatment effect estimates
- Is routinely used to inform clinical guideline recommendations, technology appraisals

Example: Headaches clinical guideline



Minimal Clinically Important Difference
(MCID) = 0.5 days per month

(NICE CG151.1, 2015)

Treatment	Mean change in headache days per month (95% CrI)
1 Placebo	0
2 Telmisartan	-0.51 (-2.32, 1.27)
3 Amitriptyline	-1.14 (-2.45, 0.16)
4 Divalproex Sodium	0.13 (-0.99, 1.23)
5 Gabapentin	0.00 (-1.60, 1.58)
6 Topiramate	-1.04 (-1.52, -0.58)
7 Propranolol	-1.19 (-2.20, -0.20)
8 Propranolol/Nadolol	-0.60 (-1.65, 0.45)

Motivation

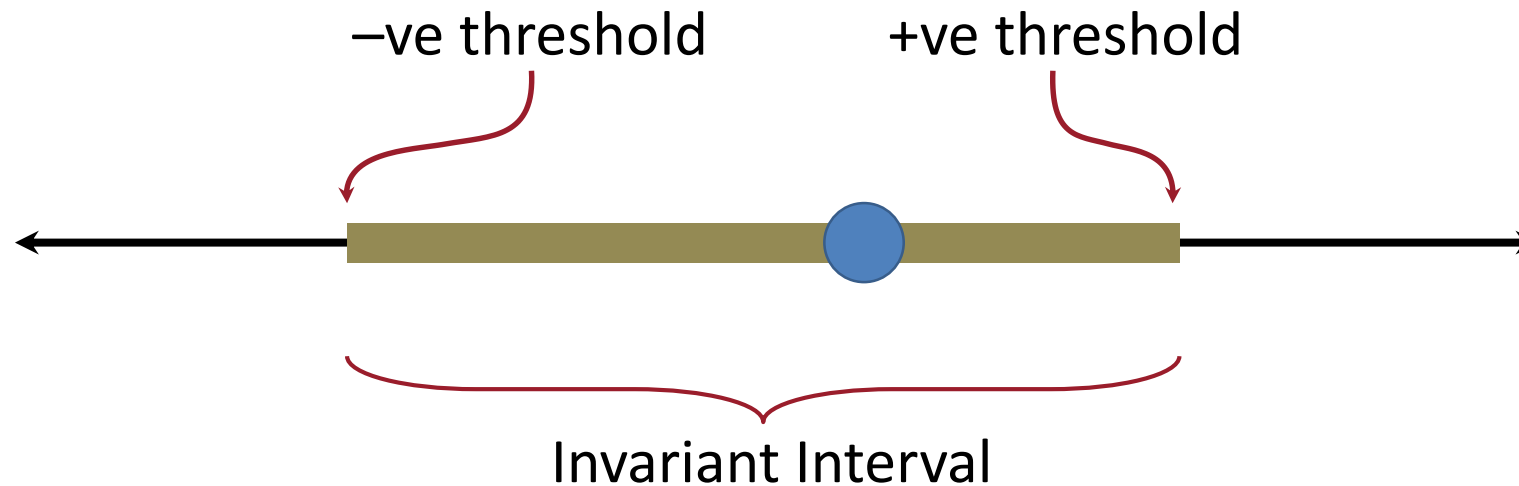
How robust are the recommendations based on NMA?

The quality of evidence reflects the extent to which our **confidence in an estimate of the effect** is adequate to **support a particular recommendation**. (*GRADE Handbook, 2013*)

		Quality	
		Low	High
Influence	Low		
	High		

Threshold Analysis

Create an *invariant interval* for a data point:



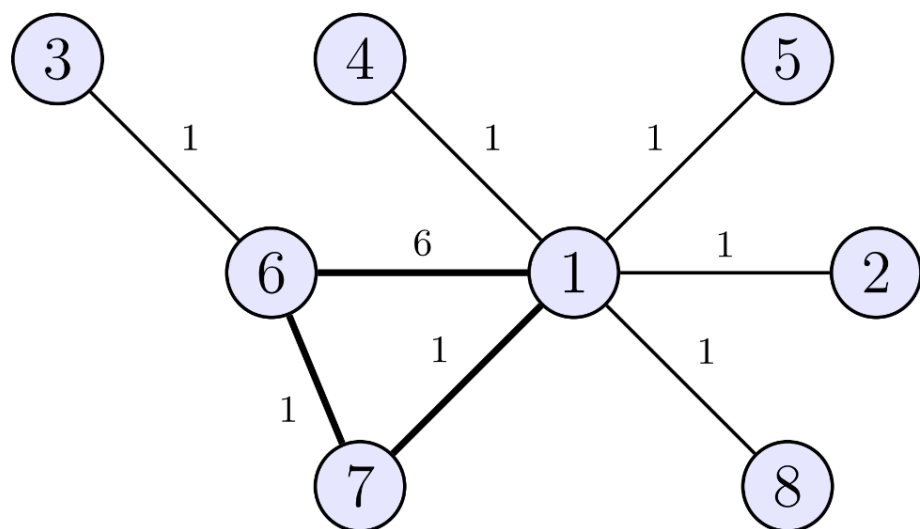
How much would the evidence have to change before we reach a new recommendation?

Threshold Analysis

We can do this at two “levels”:

- Study level
 - Thresholds for each individual study estimate
- Contrast level
 - Thresholds for combined body of evidence on a contrast
 - Highly flexible due to approximation step

Example: Headaches clinical guideline



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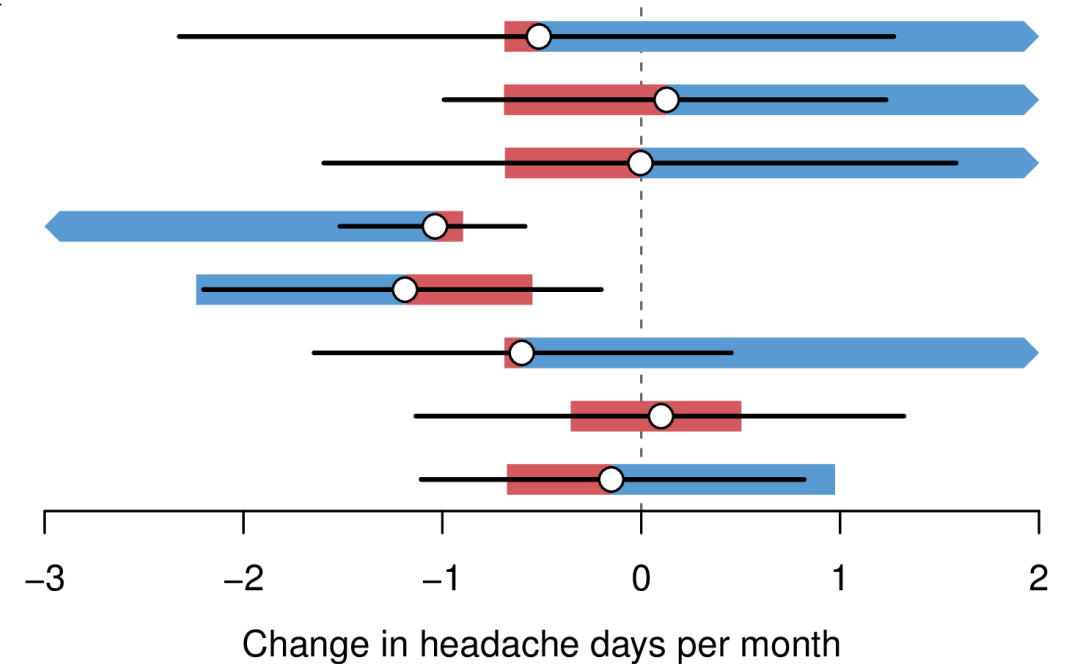
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Example: Headaches clinical guideline – contrast level

Contrast	Mean	95% CrI	Invariant Interval and \tilde{k}^*		
2 vs. 1	-0.51	(-2.32, 1.27)	2, 3, 6, 7	(-0.69, NT)	–
4 vs. 1	0.13	(-0.99, 1.23)	3, 4, 6, 7	(-0.69, 12.02)	3, 6, 7, 8
5 vs. 1	-0.00	(-1.60, 1.58)	3, 5, 6, 7	(-0.69, 24.04)	2, 3, 6, 7
6 vs. 1	-1.04	(-1.51, -0.58)	–	(NT, -0.90)	3, 6, 7, 8
7 vs. 1	-1.19	(-2.20, -0.20)	3, 7	(-2.24, -0.55)	3, 6, 7, 8
8 vs. 1	-0.60	(-1.64, 0.45)	3, 6, 7, 8	(-0.69, NT)	–
6 vs. 3	0.10	(-1.13, 1.32)	6, 7	(-0.35, 0.50)	3, 7
7 vs. 6	-0.15	(-1.11, 0.82)	3, 7	(-0.67, 0.97)	3, 6

○ Mean — 95% CrI ■ Invariant Interval

Base-case optimal treatment set is 3, 6, 7.

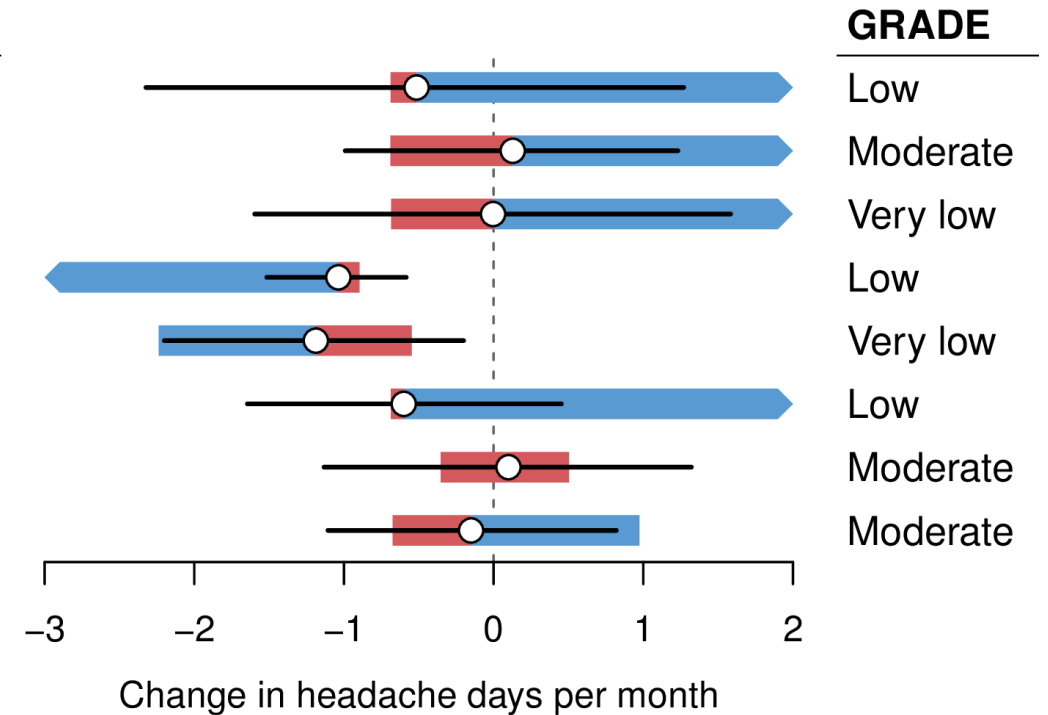


Example: Headaches clinical guideline – contrast level

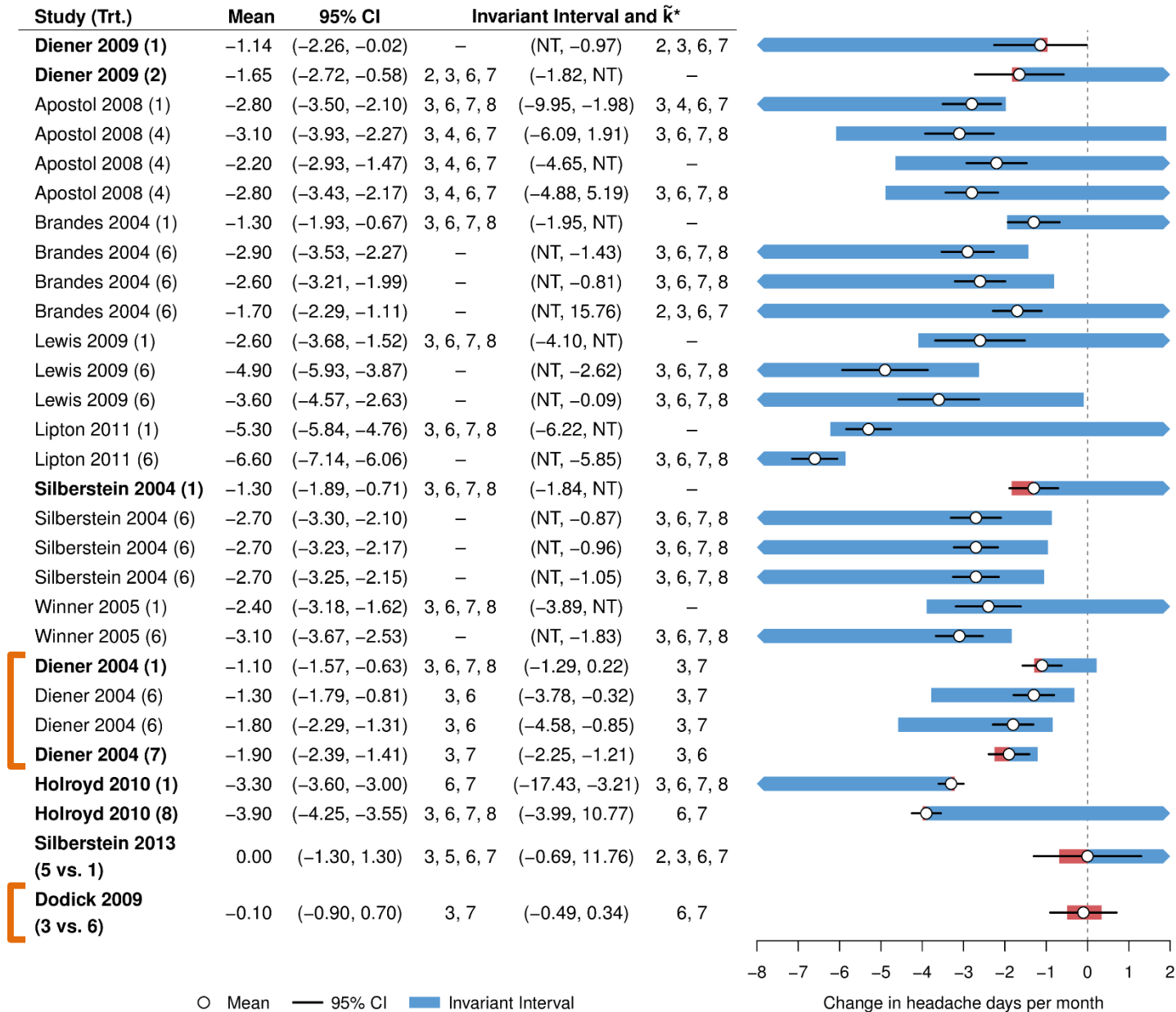
Contrast	Mean	95% CrI	Invariant Interval and \tilde{k}^*		
2 vs. 1	−0.51	(−2.32, 1.27)	2, 3, 6, 7	(−0.69, NT)	–
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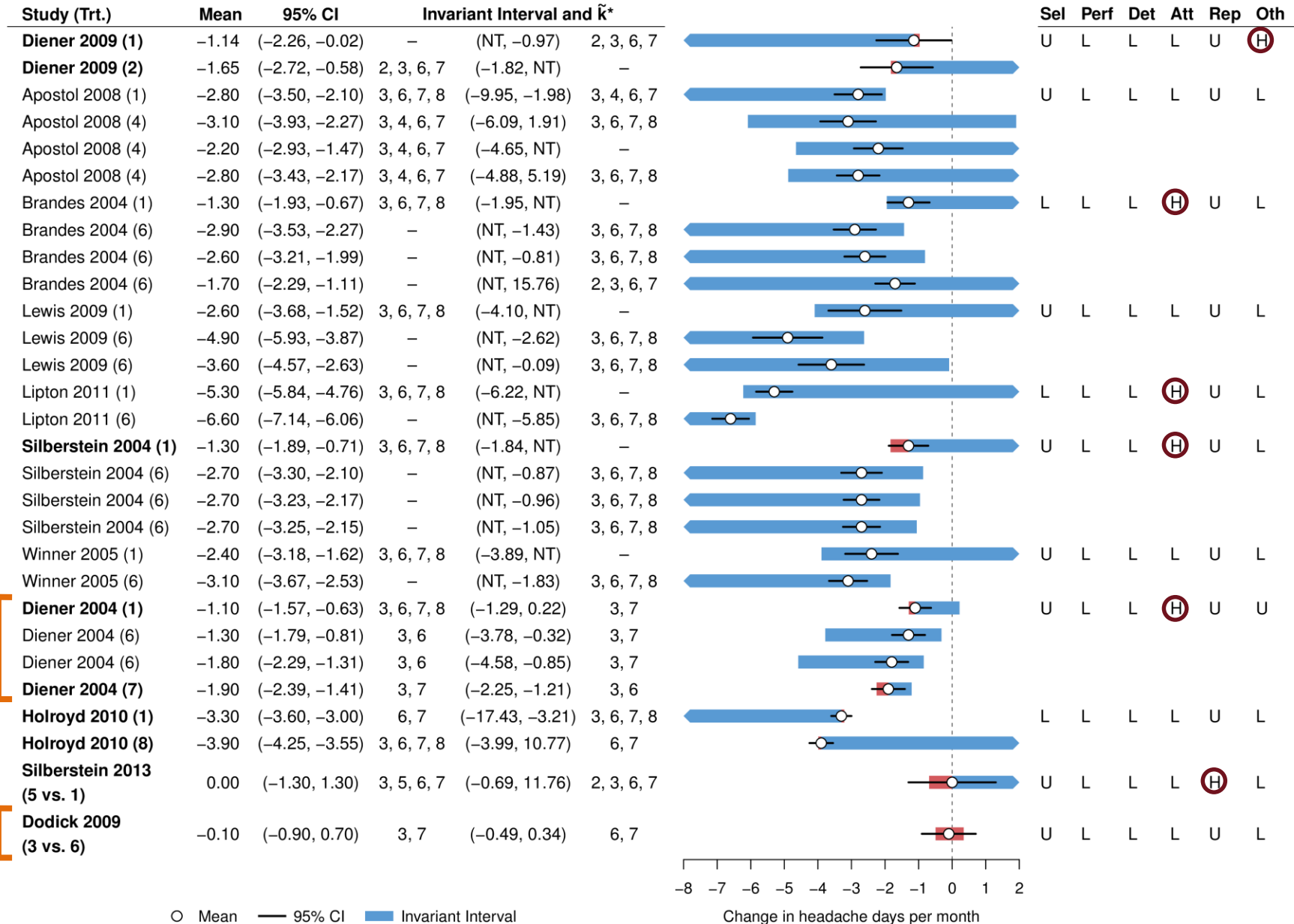
Base-case optimal treatment set is 3, 6, 7.



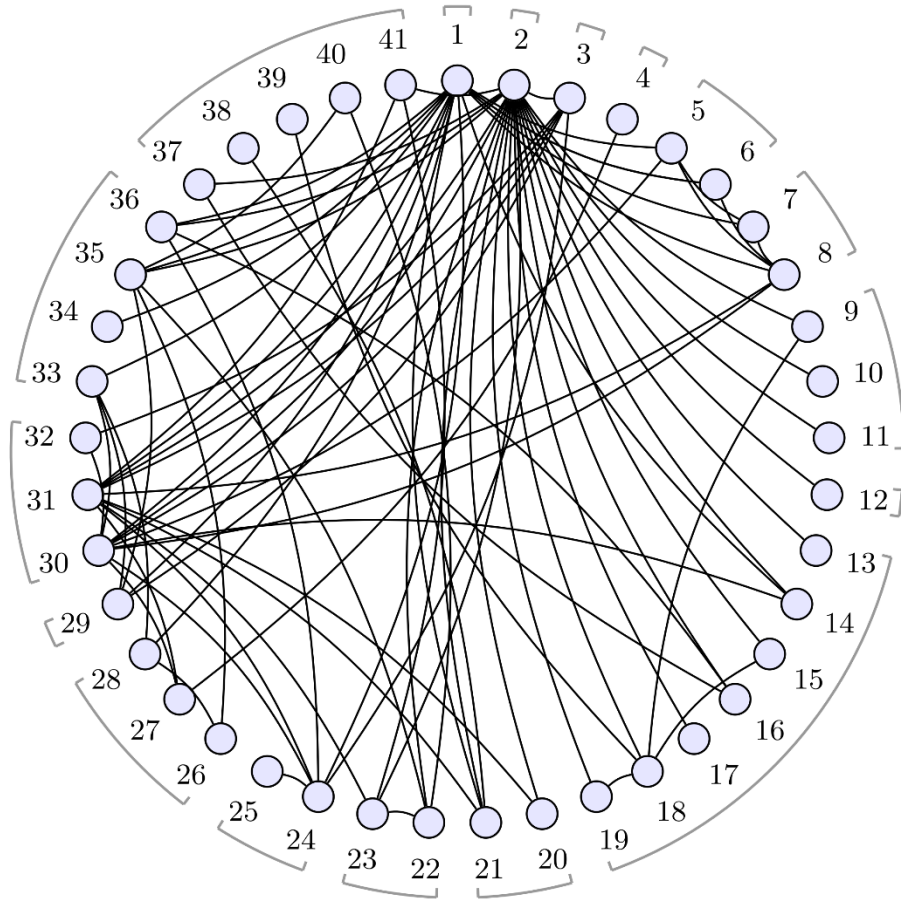
Example: Headaches clinical guideline – study level



Example: Headaches clinical guideline – study level



Example: Social Anxiety

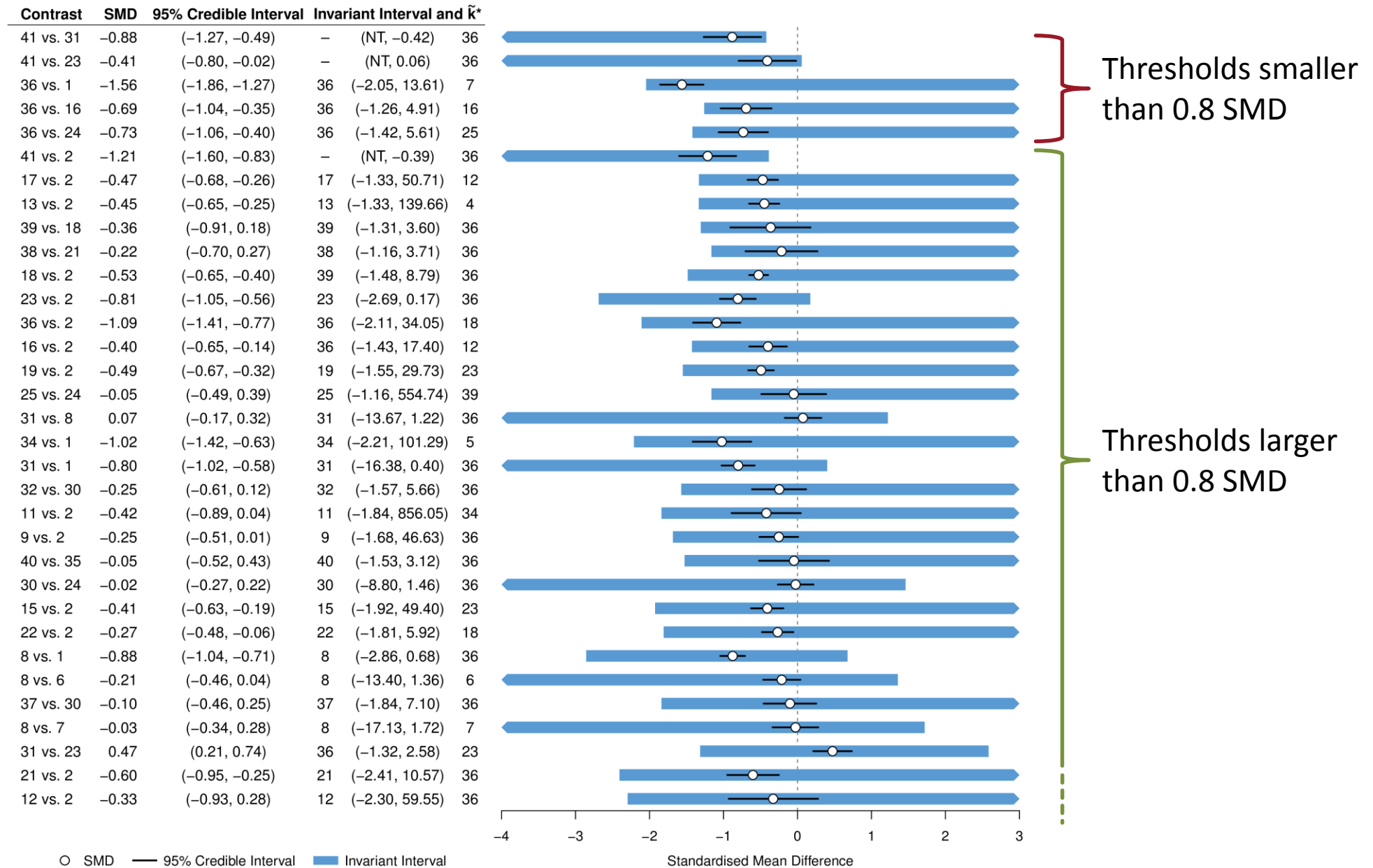


- 41 treatments, 100 studies
- Class effect model with 17 classes
- 84 direct comparisons and many “first order” loops
⇒ GRADE impractical

Based on efficacy alone recommendation is
CBT + Phenelzine (41)

(NCC-MH, 2013)

Example: Social Anxiety – contrast level



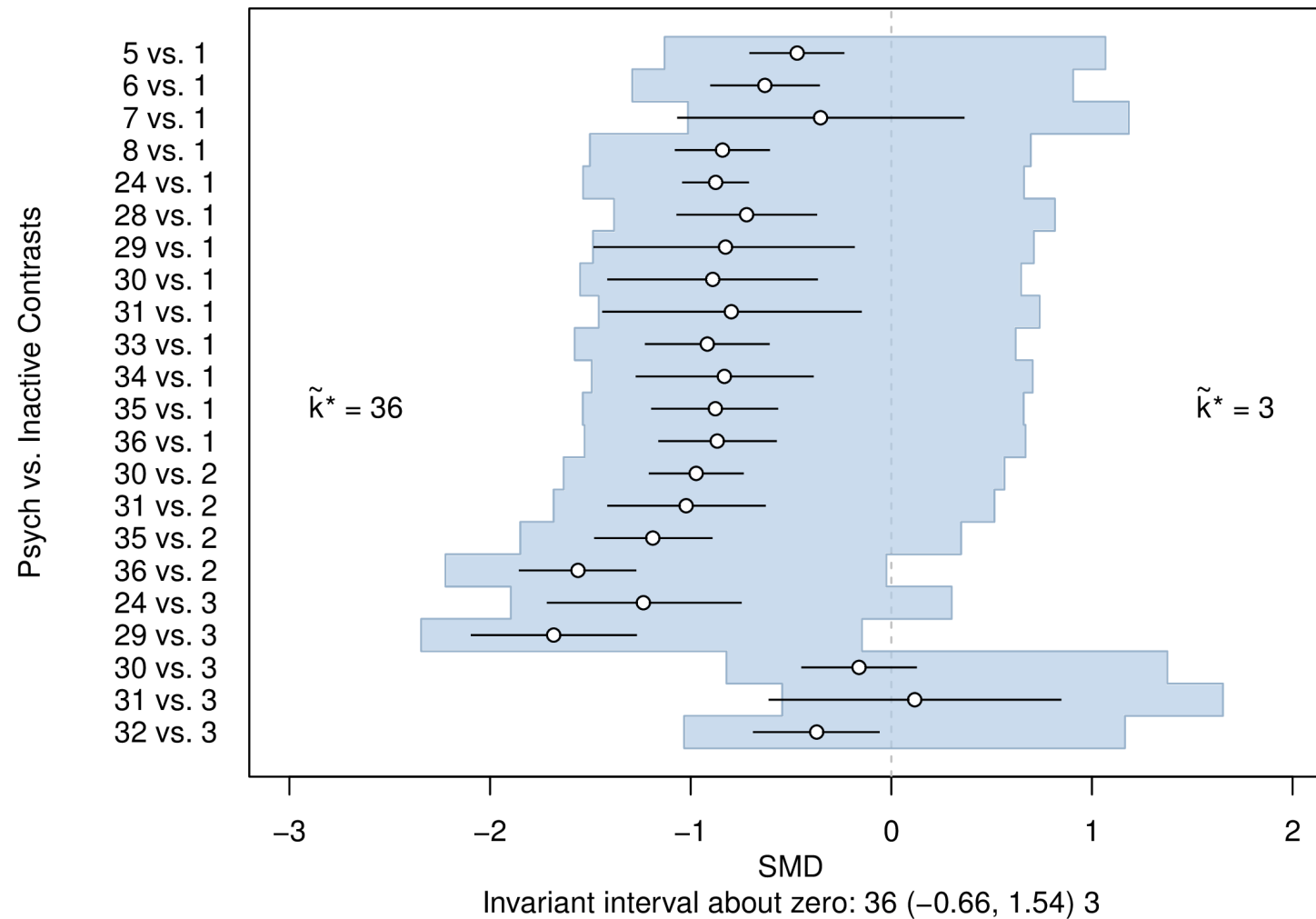
Example: Social Anxiety

We can also use threshold analysis to investigate more specific concerns

- E.g. groups of treatments or studies with certain characteristics

Psychological treatment bias – could this affect the recommendation?

Example: Social Anxiety – psychological treatment bias



Conclusions

- Evidence quality and risk of bias are not sufficient to assess robustness of decisions
- Threshold analysis provides insight into the effects of changes in the evidence on treatment decisions
 - We can have more confidence in recommendations where thresholds are large
 - We can focus attention on the quality of decision-sensitive trials and contrasts
- More complex analyses can investigate specific concerns in the evidence
- Can be used with a range of decision rules or for decisions based on cost-effectiveness

Phillippo DM, Dias S, Ades AE, Didelez V and Welton NJ (2018). *Sensitivity of treatment recommendations to bias in network meta-analysis*. J. R. Stat. Soc. A, 181: 843-867. doi:10.1111/rssa.12341

R package *nmathresh* package available on CRAN

Thank You

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MRC

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